REMARKS

Claims 1-19 have been cancelled. Claims 20-29 were pending. Claims 20-21 have been amended. No new matter is added. Applicants respectfully request reconsideration of the rejections.

Support for the amending language may be found in the specification at paragraphs 20-21.

Claims 20-27 have been rejected under 35 U.S.C. 112 as failing to comply with the written description requirement. The Office Action states that the structures of the two Bok proteins are not sufficiently descriptive of a representative number of species encompassed by the genus. Applicants respectfully submit that the present claims are enabled by the specification.

Applicants have provided mammalian Bok sequences from two different species – human and rat, and have further provided variants of Bok, in the Bok-S and Bok-L variants. In addition to the sequence disclosures, Applicants have provided guidance for one of skill in the art to screen the many available genetic resources for homologous sequences.

As set forth in the specification at paragraphs 20-21, homologs of Bok are readily identified using the provided sequences. For example, all or a part of the provided sequences can be used as a wet lab or virtual probe, in order to identify similar sequences.

Nucleic acids having sequence similarity are detected by hybridization under low stringency conditions, for example, at 50°C and 10XSSC (0.9 M NaCl/0.09 M sodium citrate) and remain bound when subjected to washing at 55°C in 1XSSC. Sequence identity may be determined by hybridization under stringent conditions, for example, at 50°C or higher and 0.1XSSC (9 mM NaCl/0.9 mM sodium citrate).

As stated in paragraph 21, between mammalian species, *e.g.* human and mouse, homologs have substantial sequence similarity, *i.e.* at least 75% sequence identity between nucleotide sequences. Sequence similarity is calculated based on a reference sequence, which may be a subset of a larger sequence, such as a conserved motif, coding region, flanking region, *etc.*

In view of the wide availability of sequence information for a number of mammalian species, there is no undue burden on the practitioner to determine a mammalian Bok sequence within the current breadth of the subject claims. Indeed, a quick BLAST alignment reveals homologs in the mouse (Genbank accession numbers BC030069.1; AF027707; NM_016778.1) as well as chicken (Genbank accession numbers AF275944 and AF290888.1); cow (Genbank accession numbers 521713; and CB772548); and pig (EMBL accession number BX917766.1).

Applicants respectfully submit that one of skill in the art can readily practice the claims as presently written. There is an overabundance of publicly available genetic sequence information, and well-known and widely used methods for screening or amplifying such sequences in order to provide the gene product(s) for use in methods such as those claimed by Applicants. In view of the above amendments and remarks, withdrawal of the rejection is requested.

Claims 20-29 have been rejected under 35 U.S.C. 112 as failing to comply with the written description requirement. The Office Action states that with respect to agents that mimic Bok function, Applicants have not provided sufficient written description to empower one skilled in the art to determine what types of compounds currently known could alter Bok function. The Office Action further states that this is a huge genus, and one would not be able to envisage the structure of agents encompassed by the claims without guidance. Applicants respectfully submit that the presently claimed invention meets the requirements of 35 U.S.C. 112.

The purpose of screening methods of the type claimed is to provide the skilled person with a means to examine large numbers of compounds, for example, using a commercial library, so as to be able to discover new and useful products that allow new treatments of disease to be developed. It is a characteristic feature of such screening methods that a large number of different compounds will need to be screened in order to identify a few compounds with the desired activity.

Given that a large number of test compounds will be screened by methods of the type described in the specification, rejection of claims to screening methods for the sole reason that the term 'compound' does not satisfy the requirements of 35 USC§112 first paragraph would render any screening method unpatentable and would represent a *de facto* bar on the patentability of screening methods, which may have great commercial value. It is respectfully submitted that there is no such bar in US law.

It may be noted that in the Trilateral Project B3b Report on Comparative study on biotechnology patent practices (Theme 'Comparative study on 'reach-through claims' (Nov 5-9 2001)), no rejections were raised by the USPTO (or any of the other offices) to the use of the term 'candidate compound' in claims to screening methods (claim 2 of cases 1, 2, 3, and 4).

For the reasons set out below, a consideration of the factors shows that the disclosure of the specification satisfies the requirements of 35 USC §112 enablement requirement, and no undue experimentation is required to practice the invention.

The Examiner suggests that, because the genus of 'compounds' is broad, it is unpredictable. This is not the case. Whilst a broad genus of compounds can be screened using the present methods, no element of unpredictability is introduced into the claimed screening methods by the

breadth of this genus. Applicants have provided a clear biological assay for the activity of Bok, *i.e.* where programmed cell death takes place, and additionally a molecular interaction, as evidenced by protein binding in the yeast two hybrid analysis. The screening method will show that the compound is active, for example by a positive signal in the yeast two hybrid analysis, or it shows that the compound is inactive. It is entirely predictable that an agent will either score as a positive in such assays, i.e. it will bind, will prevent cell death, *etc.*, or it will be inactive. A skilled person can select any member of the genus of 'compounds' in the certainty that the screening method will thus identify the compound.

In order to be screened by the present methods, the compound is not required to possess any particular properties, attributes or features: a compound of any structure may be subjected to a screening method of the invention. As no function or activity is required of the compound in order to produce an outcomes (i.e. positive or negative), there is no requirement for any degree of prediction of properties or structure before the method is performed and no 'pre-selection' is required. This is, of course, the whole point of a screening method. If a skilled person could predict in advance which compounds would be identified as active using the screening method, there would be no point in actually performing the method.

The skilled person can therefore work the invention on any member of the genus of 'compounds' without any undue experimentation – the artisan simply needs to pick a compound and perform the assay. Knowledge of chemical synthesis or modification is irrelevant to present invention. A skilled person simply takes a compound and ascertains, using a method of the invention, whether the compound is active or inactive. There is no need to design, synthesize or modify a compound to generate any particular activity or function. Compounds are screened without any prior analysis, prediction or design and the small proportion identified as 'hits' are then subjected to further optimization and development.

In summary, the broad genus encompassed by 'compound' does not automatically mean that the term is unpredictable or unenabled. In the context of a screening method, the broad definition is entirely appropriate and any limitation to a particular compound or class would be wholly arbitrary. The nature of the invention is therefore such that the scope of the term 'compound' is entirely appropriate.

Claims 20-29 have been rejected under 35 U.S.C. 112 as failing to comply with the enablement requirement. The Office Action states that the *in vitro* or *in vivo* screening for agents that mimic Bok function is disclosed, but that Applicants have not provided examples of the successful identification of a compound that can mimic Bok function; and that there is no evidence

of record to show that if such an agent is identified, it would reach its target *in vivo* and have the desired biological activity. Applicants note that Claim 21, and Claims 22-29, which are dependent thereupon, recite an agent that "binds to or interacts with said Bok polypeptide".

Applicants respectfully submit that the presently claimed invention is enabled by the specification. The specification provides experimental data, which corresponds to published articles by the inventors, Hsu *et al.* (1997) and Hsu *et al.* (1998) (copies enclosed herewith) demonstrate the structure and function of the Bok polypeptide, assays for its function, and screening for polypeptides that physically interact, and that alter the activity. In addition, and as further evidenced by the discussion of the inventors in Hsu and Hsueh (2000); a considerable amount is known about the molecular structure and function of the Bok protein.

As evidenced in the subject specification and in Hsu *et al.* (1997); Bok induces apoptosis in mammalian cells when it is over-expressed. This cellular effect, *i.e.* programmed cell death, provides one end point for assays of Bok biological activity. For example, by introducing Bok coding sequences into a mammalian cell of interest, programmed cell death will take place.

Yeast two hybrid analysis provides another exemplary assay. Two hybrid analysis was used as a screen to initially identify the Bok coding sequence. Bok was shown to interact with Mcl-1 in a protein specific binding assay, as evidenced by the results of yeast two hybrid data. Yeast two hybrid analysis was further shown to be effective in the detection of proteins that interact with Bok. Bok was shown to interact with BHRF1; Bfi-1; and was further characterized as lacking interaction with Bcl-2; Bcl-xL; and Bcl-w, (see Figure 2 of Hsu *et al.* (1997)).

As shown in Figure 3 of Hsu *et al.* (1997) there is a clear, physiologically relevant assay of Bok function, in the induction of apoptosis. Figure 4 shows the results of assays designed to screen for suppression of Bok function where, for example, BHRF1 is shown to suppress apoptosis to the level of a vector only control. Other molecules are shown to mimic Bok activity, by inducing apoptosis.

It is further shown by Hsu *et al.* (1998) that a truncated form of Bok that lacks a conserved BH3 domain can still induce apoptosis, but does not interact with anti-apoptotic Bcl2 proteins. It is demonstrated in Figure 4 of the paper that amino acid substitutions can be used to manipulate the binding activity of Bok to other proteins, without losing the cell killing properties of the protein.

As evidenced by Hsu and Hsueh (2000); and Hsu *et al.* (1998); there is considerable knowledge not only of the physiological effects of Bok, but of its structure. Figure 6 of Hsu and Hsueh provides a schematic of the molecular structure and role of Bok in forming channels in mitochondria, which then regulates apoptosis.

Applicants respectfully submit that the presently claimed invention is enabled by the specification. There are several clear assays for Bok interactions and functions, which include a yeast two hybrid assay for protein interactions, and determination of programmed cell death. These assays are shown to be effective in identifying molecules that interact (or that lack interaction) with Bok. Variations are shown where the binding interactions and physiological effects can be separately determined. Further, the molecular structure of the protein and its role in cell physiology are demonstrated and can be used to aid in assay development.

Applicants respectfully submit that practice of the claimed invention is readily undertaken and performed by one of ordinary skill in the art. In view of the above, remarks, withdrawal of the rejection is requested.

CONCLUSION

Applicants submit that all of the claims are now in condition for allowance, which action is requested. If the Examiner finds that a Telephone Conference would expedite the prosecution of this application, she is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any other fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number STAN-072CON.

Respectfully submitted,

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